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14. ABSTRACT: Utilizing a multi-dimensional research model, this study integrates biomechanical, clinical, neurobiological, and neuroradiological markers of mTBI, with the ultimate goal to more fully inform a neurobiopsychosocial model of mTBI risk, recovery and outcome. With the goal of baseline testing 900 athletes and enrolling 50 injured athletes and 50 contact and 50 non-contact controls over the course of 3 years, the project is progressing ahead of schedule and on budget. In the first 2.5 years of the study, we have enrolled 865 at baseline and accrued 86 concussed athletes in the multidimensional postinjury protocol, along with 99 non-injured control athletes. All groups are undergoing follow up evaluations within 6 hours of injury, 48 hours after injury, and 8, 15, and 45 days after injury. These evaluations include advanced brain neuroimaging, blood biospecimen collection, and clinical testing measures assessing balance, neurocognition, symptoms, and psychological health, which will be correlated with data from the Head Impact Telemetry system (HITS). Several lines of preliminary analysis have been presented at national research meetings, submitted for publication or are in preparation for peer-review. Further data analyses are underway, with our investigative team developing advanced database platforms and analysis techniques. Major progress has been achieved with regard to an advanced platform and "pipeline" for MRI data processing, quality control and integration. Ongoing collaboration with co-investigators and our project partners has guided us to a successful launch of this comprehensive study, which will lead to advancing the science of mTBI and improving clinical care in military, sports, and civilian populations. This project's focus on high school and lower level collegiate athletes makes it fully distinct from the NCAA-DoD CARE Consortium. The combined findings from this study are predicted to have major translational impact on the science and clinical care for concussion in all populations, including the settings of military medicine and civilian trauma.

15. SUBJECT TERMS
Traumatic brain injury, concussion, biomechanics, head impact measurement, neuroimaging, biospecimens, neurobiopsychosocial

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1. INTRODUCTION:

During the acute phase, mild traumatic brain injury (mTBI) is known to cause serious disruption in normal biological, cognitive, and behavioral function. While research over the last decade has significantly advanced the science of mTBI, a comprehensive neurobiopsychosocial model of mTBI has yet to be achieved. With the goal of conducting a comprehensive study of mTBI, we hypothesize that there will be a significant correlation between biomechanical, clinical, neurobiological, and neuroradiological markers of mTBI, which will more fully inform a neurobiopsychosocial model of mTBI. The overarching aim of this proposal is to investigate the predictive and correlative value of multiple diagnostic and prognostic markers of mTBI in a common injured sample and single study design, including:

- Advanced brain neuroimaging to study changes in brain structure and function
- Blood biomarkers to study changes in brain biochemistry and physiology
- Head impact sensor technologies to study the kinetics and kinematics of concussion and the effects of repetitive, subconcussive head impacts
- Genetic testing to study the influence of genetics on risk of mTBI and post-concussive recovery
- Clinical measures of postconcussive symptoms, neurocognition, balance, psychological health, and other functional capacities to correlate with neurobiological, neuroimaging, biomechanical and genetic markers of injury

Please see section 9 (Appendices, Table 2) for a more detailed summary of this study's technical objectives and specific scientific aims.

2. KEYWORDS:

Traumatic brain injury, concussion, biomechanics, head impact measurement, neuroimaging, biospecimens, neurobiopsychosocial

3. ACCOMPLISHMENTS:

What were the major goals of the project?

The major tasks of this project are designed to successfully achieve the specific technical objectives and scientific aims of the study (see Appendices). Please find below a summary of the major tasks, projected timeline, level of completion as of the current reporting period, in accordance with the approved Statement of Work (SOW).

We have completed a significant amount of work toward accomplishment of the major tasks and subtasks for the current reporting quarter and year, as described below. The major tasks and subtasks for this project are also being coordinated and completed in sequence with planning and execution of the NCAA-DoD Grand Alliance Advanced Research Core (ARC), given the scientific and operational benefits of synchronization between the two projects.

Major Tasks from Statement of Work (SoW)	Timeline (months)	Date or % of completion
Major Task 1: Finalize Project Contracting, Regulatory, and Operational Processes	1-6	100%
Major Task 2: Operationalize Protocol to Achieve Specific Aims (SA) and Technical Objectives 1-4	1-6, Ongoing	90%
Major Task 3: Data Collection (post-IRB approval)	7-48	80%
Major Task 4: Data Management, Analysis & Dissemination	1-48	50%

What was accomplished under these goals?

The tables below provide an update on the status of our progress associated with each of the Major Tasks and Subtasks for the project, in accordance with the approved SoW for this project.

Major Task 1: Finalize Project Contracting, Regulatory, & Operational Processes	**Months 1-6**

Subtask 1 - Contracting

- Renewed Banyan Biomarkers subcontract through December 31, 2017
- Received Modification #3 on December 29, 2016 that incorporates a slightly revised SOW

Subtask 2 – Human Subjects Research

- Annual Continuing Progress Report approved by MCW IRB on March 14, 2017
- HRPO acceptance of MCW Continuing Progress Report on April 17, 2017

Subtask 3 – Project Staffing and Operations

- Evaluating staffing levels for Summer/Fall 2017 baseline testing
- Staff hired and trained for 2017 baseline testing and post-injury data collection

Subtask 4 – Project Management

- Standing weekly laboratory meeting to facilitate project planning and monitor progress continued
- Additional meetings with core subject matter experts occurring at regular intervals to ensure consistency with ARC protocol, plan for data dissemination, and plan for data pipelining
- Annual investigator meeting held on May 4-5, 2017 at the Medical College of Wisconsin
- PI presented at JP6 IPR on June 6, 2017

Major Task 2: Operationalize Protocol to Achieve Specific Aims (SA) and Technical Objectives 1-4	**Months 1-6**

Subtask 1 – Overall Protocol Implementation and Management

- Overall, the project is progressing on schedule and on budget.
- Baseline testing dates occurred for Fall 2017 between June 28, 2017 and August 17, 2017
- Total baseline enrollment is up to 1,154 athletes
- 594 athletes are active under protocol for Fall 2017, including 320 athletes equipped with the Head Impact Telemetry System (HITS) and 28 equipped with the Prevent Mouthguard
- To date, 86 athletes with concussion were enrolled into the post-injury protocol; an additional 99 non-concussed controls have been enrolled in the parallel protocol.
- Project updates at JPC-6 Combat Casualty Care In-Process Review (IPR) meeting, Ft. Detrick, June 6, 2017

Subtask SA1 – Advanced Neuroimaging Protocol

- Continued development of a robust MRI Informatics Core function at MCW to support pre- and post-processing, advanced algorithm development, analysis pipelines, data scaling techniques, etc. to support this and other studies
- Radiology team following protocol to review MR for incidental findings
- Continued collaboration with GE to implement latest GE TBI research protopak 2 for GE 750 3.0T MRI at MCW
- In collaboration with NCAA-DoD CARE Consortium Advanced Research Core (ARC), significant progress on all aspects of the pipeline augmentation to support quality control and advanced pre- and post-processing methodologies and analytics
- Priorities for further MRI data analysis and publications identified and in progress
- Interim data analysis have been presented at national meetings and prepared for peer-review, with a focus on advanced MRI methodologies and translational impact of MRI findings on understanding neurobiological effects and recovery after concussion.
- Bi-weekly meetings with MRI Core imaging investigator team to ensure consistency with ARC protocol, plan for data dissemination, and plan for data pipelining
- Continued refinement and optimization of pipeline for quality control and analytics for neuroimaging data acquisition, processing, transfer, storage, integration with larger dataset, analysis and dissemination, which includes implementation of XNAT database and use of Isilon server
- Discussions with GE Healthcare Global Research Center investigators on how to leverage their work and this project to advance TBI neuroimaging technology development and wider implementation for clinical use

Subtask SA2 – Blood Biomarkers

- Continued meetings with MCW CTSI Translational Research Unit (TRU) to ensure biospecimen team coverage during assessment time points
- Continued correspondence with Banyan Biomarkers and MCW CTSI TRU to ensure all supplies, protocols, and staffing plans are in place for baseline and postinjury testing

- Ongoing biomarker analysis being conducted in parallel to ARC analysis in Division I college athletes
- Findings from first flight of biomarker analysis, comparing concussed and control athlete levels at baseline and during the acute phase (<6 hours and 24-48 hours postinjury) are published in Journal of Neurotrauma [Epub ahead of print].
- Next phase of targeted biomarker analysis was completed and preliminary results were presented at the 2017 Investigator Meeting; results are under analysis and preparation for peer reviewed publication
- Discussions with Dr. Jessica Gill from the NIH on engagement in our biomarker work, in parallel to her direct involvement in the CARE Consortium ARC biomarker core team.
- Additional priorities for further biomarker data analysis in progress, including future analysis of targeted biomarkers and possible opportunities for novel biomarker discovery
- Future plan for integrated analysis to correlate biomarker data with clinical, neuroimaging and head impact data elements

Subtask SA3 – Head Impact Sensors

- Continued collaboration with ARC Head Impact Measurement (HIM) core team around plan for testing and deployment of non-helmeted sensors so to identify technologies fit for research data collection across the current study and ARC
- HIM data analysis being conducted in parallel to ARC analysis in Division I college athletes
- Continued engagement of MCW investigators key to head impact measurement element of study in planning around Pipeline Model for head impact measurement data acquisition, processing, transfer, storage, integration with larger dataset, analysis and dissemination
- Developing stepwise approach to head impact measurement data analysis based on pre-defined hypotheses, core metrics, and analytical methods
- Conducting bi-weekly sessions with HIM team members to do detailed review of head impacts recorded in concussed athletes to assist in correlating HITS data with other study elements (clinical, neuroimaging, biomarker, genetics)
- A modular rigid-arm pendulum capable of reaching velocities up to 11 m/s was constructed for laboratory testing and validation of candidate head impact sensors systems. Preliminary testing of the pendulum was performed by conducting a standard impactor test in accordance with NOCSAE standards on a Riddell Speed Helmet equipped with Head Impact Telemetry System (HITS).
- Dental impressions and ear molds were taken on two cadavers to manufacture custom mouth guards (Prevent Mouthguard), dental retainers (Wake Forest), and in-ear sensors (DASHR) for laboratory testing. Custom sensors were received for DASHR and Prevent in late September.
- Specimen preparation was conducted in the last week of October 2017 with testing scheduled for first week of November 2017. Prevent Mouthguard, MvTRAK (DASHR) ear sensor, HITS helmet sensor and X2 Biosystems xPatch skin patch will be compared to a reference sensor. Specimen will be tested at multiple locations and velocities to simulate head impacts seen during routine football practice/game.

- Data analysis from Fall 2016 rollout of Prevent Mouthguard sensor system (Cleveland Clinic) demonstrated an ability to collect true positive head impacts, verified using video evidence obtained during practice and game activities
- In-depth analysis of sensor accuracy is ongoing in collaboration Prevent, consisting of a head-to-head comparison of HIT System data to Prevent mouthguard data with comprehensive video analysis of all collected head impacts.
- Interim anlaysis of HIM data have been presented at national meetings and prepared for peer review, focused on the confluence of injury biomechanics and repetitive head impact exposure influencing risk of concussion.
- Priorities for further HIM data analysis, publications and dissemination identified and in progress

Subtask SA4 – Genetic Testing

- Finalized protocol on DNA extraction by engaging MCW Tissue Bank services for extraction and Indiana University for consultation and analysis, IBC, IRB, and HRPO approved
- Coordinated genetics protocol elements, data processing, pipeline and analytics with ARC
- Samples from fall 2015, 2016 and 2017 baseline testing processed and stored locally; will wait until the end of baseline data collection for group analysis

Major Task 3: Data Collection (post-IRB approval)	**Months 7-48**

Subtask 1 – Baseline Data Collection Protocol

- Successful baseline data collection on 254 athletes for the Fall 2017 season, bringing total baseline enrollment to 1,154
- 594 athletes are active under protocol for Fall 2017, including 320 athletes equipped with the Head Impact Telemetry System (HITS) and 28 equipped with the Prevent Mouthguard

Subtask 2 – Postinjury Data Collection Protocol

- To date, 86 athletes with concussion were enrolled into the post injury protocol
- Attrition rate is low (8.8%) with 77 missed visits out of 874 between injured and control groups, including injured subjects who missed a 6 hour evaluation due to late reporting (see Table 3)
- Injury accrual is ahead of schedule with a total of 86 concussed subjects enrolled and followed in the post-injury protocol (target accrual at this point: 45); this is achieved on budget and will allow oversampling to provide adequate statistical power to enable more complex analyses of associations between data elements (e.g., clinical, blood biomarkers, MRI, head impact measurement).

Subtask 3 – Control Group Testing

- To date, 99 non-concussed controls have been enrolled in the parallel follow-up protocol

- Recruitment of both contact and non-contact sport controls is on schedule, concurrent with the concussed cohort. We anticipate no issues in reaching our targeted endpoints for both contact sport and noncontact sport controls

Major Task 4: Data Management, Analysis & Dissemination	**Months 7-48**

Subtask 1 – Data Management

- Data quality control plan reviewed and revised from existing procedures to handle all data elements
- Finalizing plan for integration of core data elements from all protocol components (neuroimaging, head impact measurement, biomarkers, genetic testing) with clinical data in REDCap database
- Finalizing plan for connectivity between central REDCap database and repositories holding larger raw data sets from all protocol components (neuroimaging, head impact measurement, biomarkers, genetic testing)
- Finalized development of separate databases and repositories to hold larger raw datasets from neuroimaging and head impact measurement cores
- Core data elements for current study continually cross-walked with ARC as changes in ARC occur
- Continued engagement with Federal Interagency TBI Research (FITBIR) Informatics System to discuss data submission for head impact measurement data, MR data, and biospecimen data
- Work under way with FITBIR Ops Team for curation and transfer of imaging and biomarker data to FITBIR
- Study PI (McCrea) a member of the NINDS working group for formation of Common Data Elements (CDE) for sport-related concussion. Case Report Forms (CRF) and information on database structure from this study provided to NINDS to facilitate the CDE project.
- The following data was uploaded to FITBIR over the past year:
    - Q1 – Biomarker data from Fall 2015 season and additional Fall 2016 clinical baseline data
    - Q2 – Fall 2016 post-injury clinical data for injured athletes and contact controls
    - Q3 – Clinical data from all non-contact controls enrolled to date
    - Q4 – Fall 2017 clinical baseline data and biomarker data from Fall 2016

Subtask 2 – Data Analysis

- Ongoing analysis of clinical, imaging, biomechanics and biomarker data underway
- Continued development of pre-defined core metrics and analytical plan to test specific hypotheses within each study core (clinical, head impact measurement, neuroimaging, blood biomarkers, and genetic testing)
- Preliminary findings presented at IPR in June 2017
- Preliminary findings from this study (MRI, HIM, clinical, biomarkers) have been presented at national meetings, prepared for peer review, with further analysis underway in preparation for publication.

Subtask 3 – Dissemination

- The multidimensional and comprehensive research design employed by this study and select preliminary findings have been presented at multiple national and international forums on traumatic brain injury and sport-related concussion over the past year. Please see list of publications and presentations in section 6 (Products) below.
- As follow-up to the June 2017 IPR, our investigative team is collaborating with researchers and staff at Defense Veterans Brain Injury Center to produce a comprehensive review on acute effects and recovery after mTBI, highlighting new learnings from the current study and with a main focus toward clinical translation in military, sports and civilian medicine.
- Continued meetings and discussions with subject matter experts and investigative team to develop analytic plan for dissemination
- Manuscript priority list developed with focus on "early win" publications from data across all modalities (clinical, neuroimaging, biomarkers, head impact measurement)

What opportunities for training and professional development has the project provided?

Nothing to Report

How were the results disseminated to communities of interest?

Nothing to Report

What do you plan to do during the next reporting period to accomplish the goals?

As follow-up to the June 2017 IPR, our investigative team is collaborating with researchers and staff at Defense Veterans Brain Injury Center to produce a comprehensive review on acute effects and recovery after mTBI, highlighting new learnings from the current study and with a main focus toward clinical translation in military, sports and civilian medicine.

To continue our on-time progress toward accomplishment of the major tasks and subtasks for this project, we plan and will prioritize the following objectives during the next reporting period:

1. **Advanced Neuroimaging Protocol:**
    a. *Imaging Pipeline:* We will continue to refine the pipeline for neuroimaging data processing, transfer, storage, quality control, integration with larger dataset, analysis and dissemination continuously to ensure accuracy. A more robust technology cluster is being leveraged for more efficient and accelerated data processing capabilities.
    b. *Analytics*: We will continue with our a stepwise approach to neuroimaging data analysis based on pre-defined hypotheses, core metrics, and analytical methods to achieve our specific aims, with focus on early win manuscripts. Targeted findings will be prepared for dissemination as abstracts and publications.
    c. *Radiology*: Incidental findings will be further evaluated to assess incidence rates and possible relation to mTBI.

2. **Blood Biomarker Protocol:**

    a. *Analysis*: Results from the second flight of biospecimen analyses are being prepared for publication. Preliminary results from these analyses were presented at the 2017 investigator meeting.
    b. *Analytics and Dissemination*: Our first manuscript on the initial biomarker findings from the study has been published. We will continue our stepwise approach to biomarker analysis based on pre-defined hypotheses, core metrics, and analytical methods to achieve our specific aims.

3. **Head Impact Measurement Protocol:**

    a. *Non-helmeted Sensor Technology:* We will continue analysis of the data collected with the Cleveland Clinic Prevent Mouthguard during the fall 2016 season, and collect additional data in 28 athletes during the fall 2017 season. Data were collected using the Prevent and HIT Systems and head-to-head comparisons will be performed with regard to the frequency and severity of head impact exposure.
    b. *HITS*: We will continue data collection using the Riddell Speed and SpeedFlex helmets and sensors during the fall 2017 season.
    c. *Pipeline*: We will further operationalize the pipeline model for head impact measurement data acquisition, processing, transfer, storage, integration with larger dataset, analysis and dissemination prior to implementation to ensure accuracy.
    d. *Quality Control:* We will continue to maintain and further refine a multi-level protocol for monitoring and evaluating data quality.
    e. *Analytics and Dissemination:* Analysis and dissemination efforts will continue toward defining the biomechanics of concussion and the role of sub-concussive head impact exposure in the onset of concussion. Targeted early win publications will be prepared for publication.
    f. *Laboratory Validation:* We will perform experimental studies designed to quantify the accuracy of available head impact sensor technologies. Validation testing of head impact sensors using cadaveric specimens will initiate during November 2017. The study protocol will include the HITs helmet-based sensor system as well as the Prevent Mouthguard and DASHR ear-based sensor systems.

4. **Genetic Testing Protocol:**

    a. *Analytics*: We will continue development of a stepwise approach to genetic analysis based on pre-defined hypotheses, core metrics, and analytical methods to achieve our specific aims. Analyses to be completed closer to the end of the study, based on accumulating sample size and the importance of efficient management of study resources.

5. **Postinjury Data Collection:**

    a. *Contact Sport and Non-Contact Controls*: We will continue with our ongoing recruitment of contact sport controls and do our heaviest recruitment of non-contact sport controls in the winter and spring sports seasons. We do not anticipate any difficulty meeting our targeted samples size for the control groups.

6. **Data Management:**

   a. *Database*: We will continue to refine the architecture and function of our electronic REDCap database according to the protocol specification and required data elements, in parallel to the same for the ARC, in compliance with the NINDS CDE and in working with FITBIR for data transfer.
   b. *FITBIR*: We will continue to work on data submission for clinical and quantitative blood biomarker data. Additional discussions are underway with FITBIR to develop the transfer of imaging and head impact sensor data.
   c. *Quality Control*: We will continue to develop and implement processes to monitor data quality associated with all aspects of the protocol (clinical testing, head impact measurement, neuroimaging, biomarkers, genetic testing).

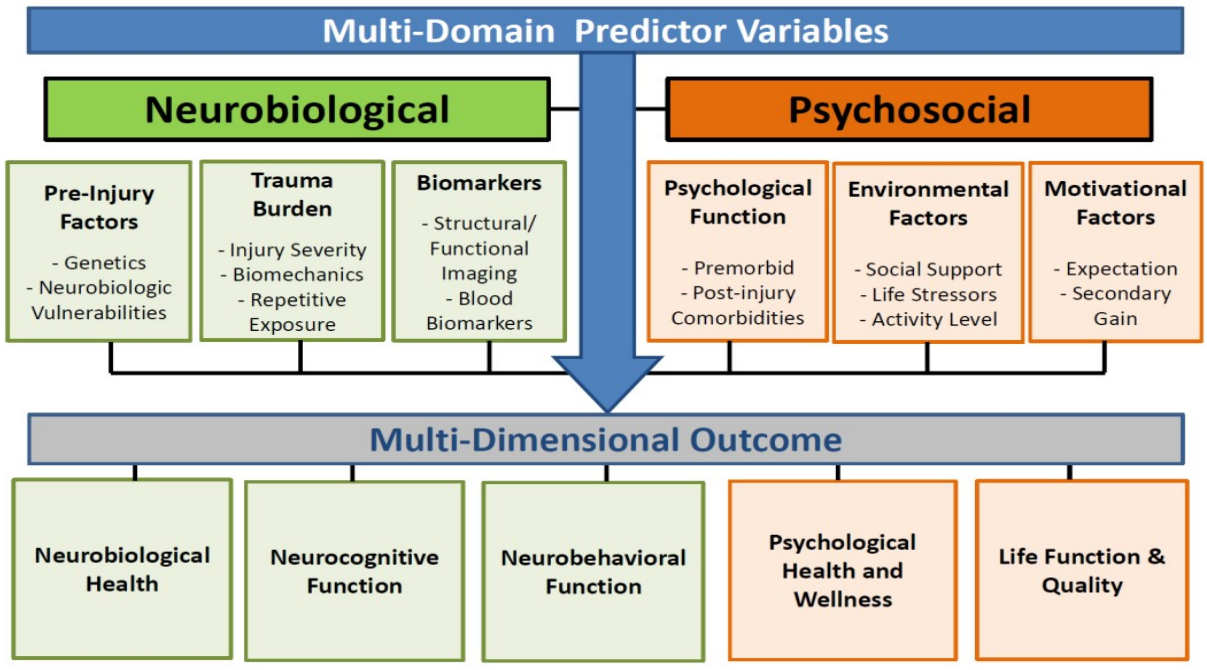
4. IMPACT:

What was the impact on the development of the principal discipline(s) of the project?

COMPREHENSIVE APPROACH TO STUDY OF TBI

Most importantly, this study will allow us to investigate the correlation between multi-dimensional predictor and outcome variables associated with mTBI from a fully neurobiopsychosocial perspective *in a common injured sample and single study design* (see **Figure 1**). This work will enable a longitudinal perspective on factors that influence both short-range and long-term outcomes after mTBI, and will foster DoD-funded collaboration aimed at informing the broader science of mTBI in military, sports and civilian populations.

Figure 1. Neurobiopsychosocial Model of mTBI



ADVANCED TECHNICAL DEVELOPMENT:

Our investigative team of TBI researchers and imaging scientists has collaboratively developed a cutting-edge, multi-modal MRI protocol targeted specifically at the pathophysiology of SRC and mTBI that will provide benefit to the TBI research community.

Our MRI protocol combines conventional anatomical imaging with advanced, motion compensated MRI acquisition techniques, diffusion kurtosis/tensor imaging (DKI/DTI), susceptibility weighted imaging (SWI) and quantitative susceptibility mapping (QSM), resting state metrics of functional connectivity (rs-fMRI), and blood flow imaging with arterial spin labeling (see **Table 1**). The protocol features a multi-band (8x) accelerated pulse sequence that achieves a high sampling rate while retaining high spatial resolution (2mm isotropic) for robust signal detection in rs-fMRI that is consistent with acquisitions in Human Connectome Project related studies. In addition, we have deployed three advanced pulse sequences and associated innovative data processing and modeling tools that show promise as diagnostic and prognostic biomarkers for diffusion kurtosis imaging (DKI), quantitative susceptibility mapping (QSM), and 3D arterial spin labeling (ASL).

Table 1. MCW Multi-Modal MRI Protocol for Acute Sport-Related Concussion

Targeted Modality	**Acquisition Protocols**	**Reconstruction Requirements**	**Acquisitio Time**
	Localizer	Standard	0:30
	Sensitivity map generation	Standard	0:30
Cerebral blood flow	3D enhanced ASL prototype	Standard, flow, transit time corrected flow	4:36
Micro hemorrhage & gray-white matter transition	SWI/QSM (2x1 ARC) prototype	Standard SWI, offline "Orchestra" phase-based imaging and QSM	4:00
Anatomy, gray-white matter segmentation	PROMO MPRAGE prototype	Standard	4:11
Anatomy, edema detection	PROMO T2 FLAIR prototype	Standard	4:42
Anatomy, pial surface segmentation	PROMO T2 prototype	Standard	4:12
White matter integrity & microstructure	DTI/DKI DTI-Distortion Cal	Standard DTI, offline post-processing of DKI from standard DICOM images, including distortion correction	5:30 0:30
Resting state functional connectivity	rs-fMRI with multi-band prototype acquisition (human connectome project harmonized) rs-fMRI-Distortion Cal	Offline "Orchestra" multi-band reconstruction (auto-calibration, slice-GRAPPA unaliasing) Offline, used for rs-fMRI distortion correction	6:00 0:30
Myelin mapping	Inhomogenous broadened magnetization transfer (IhMT) prototype	Standard, quantified MT, quantified IhMT	4:48
		Total Acquisition Time:	40:00

The technical implementation of this innovative TBI imaging protocol has been highly successful based on:

- *Engagement*: This project represents a major collaborative, multidisciplinary effort by highly skilled imaging and neuroscience researchers at MCW.
- *Scanning time*: 40-minute acquisition time.
- *Compliance*: Athletes respond favorably to the procedures and short scanning session.
- *Quality Control*: High resolution imaging with minimal technical error or artifact.
- *Automation*: Customized protocol is essentially a turn-key option for scanner operators.
- *Analytics*: Customized analysis procedures unique to each pulse sequence and modality.
- *Translation*: Targeted modalities and pulse sequences capable of rollout in clinical settings.

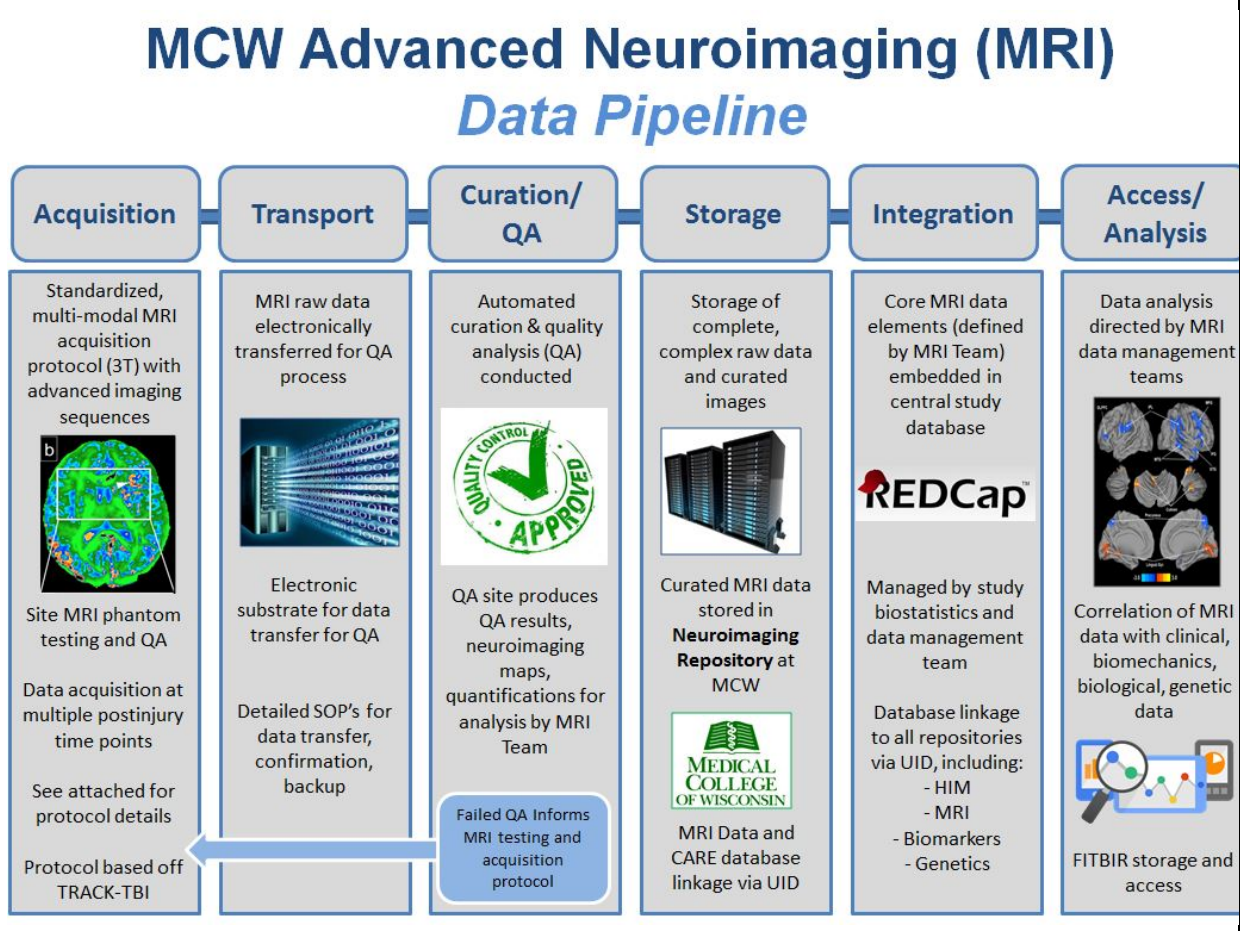
We have cross-walked our MRI acquisition protocol with the GE Research Protopak I/II for TBI and the acquisition protocols for other large research networks such as TRACK-TBI (G. Manley, PI) in order to facilitate eventual sharing/merging of like-set imaging data and enable comparisons of TBI imaging biomarkers across populations at risk (civilians, athletes, military service members). This exercise indicates a high degree of overlap between study protocols. We have merged our acquisition developments with the GE Healthcare traumatic brain imaging "Protopak 2" content to further build cross-study compatibility. This paves the way for further optimization of innovative MRI protocols to be included in other large-scale, national TBI research efforts (e.g., NCAA-DoD Grand Alliance).

POWERFUL IMAGING PIPELINE AND INFORMATICS PLATFORM

Our work supported the development and construction of a technologically advanced platform for MRI post-processing, analytics, transfer and storage that provides a powerful engine to support and accelerate our future research efforts toward advancing the science and clinical utility of MRI biomarkers for concussion and TBI.

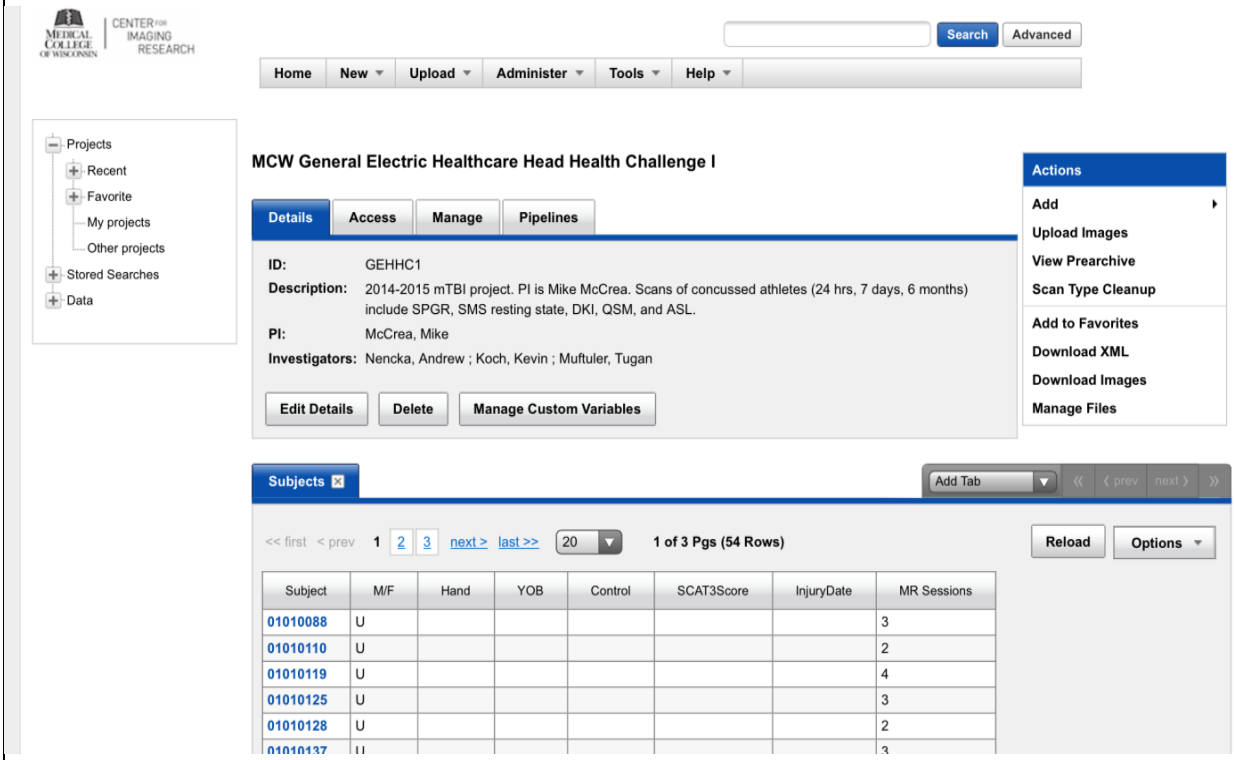
Although not initially proposed in this work, the development of an imaging informatics infrastructure has been part of this first year's progress. Each imaging session includes 12 series, 11,130 images, and over 10 gigabytes of data. Further, a subset of the prototype acquisitions, including the simultaneous multi-slice resting state fMRI and the quantitative susceptibility mapping series require off-line reconstruction of the raw k-space "p-files." With enrollment proceeding as expected and four imaging sessions for each subject, along with a large group of collaborating investigators, a central, organized, automated, and accessible database solution was required. **Figure 2** illustrates the stepwise architecture of our "pipeline" for imaging acquisition, transport, curation and quality control, storage, analysis and integration with other rich clinical datasets (see **Figure 2**). This approach was modeled after centers leading other large research efforts employing advanced MRI in the study of concussion and TBI, such as TRACK-TBI (G. Manley, PI).

Figure 2. MCW Advanced Neuroimaging Pipeline



The eXtensible Neuroimaging Archive Toolkit (XNAT, www.xnat.org) was selected to serve as the central repository for this work (**Figure 3**). XNAT offers a number of compelling features that make it ideally suited for this job. A web-based user interface facilitates team member access to the repository, which is organized hierarchically by project, subject, session and series. DICOM images acquired on the research-dedicated MCW Discovery MR750 can be directly pushed to a DICOM listener integrated into the XNAT deployment, and then automatically integrated into the image database, or archived data sets may be uploaded through the web interface. Underlying the web interface is a PostgreSQL database that can be accessed through a representational state transfer application program interface (REST API). This powerful architecture enables programmatic queries of the image and metadata database and scripting of custom processing pipelines. We have built a Python interface for scripting XNAT processing through the REST API. Work is ongoing to further integrate raw "p-file" storage and automatic Orchestra-based p-file reconstruction via "son of recon" programs automatically initiated by the acquisition pulse sequence through this XNAT REST API. While processing pipelines are prototyped outside of the XNAT framework, finalized pipelines are to be integrated into the XNAT service to further streamline data processing.

Figure 3: MCW XNAT Web Interface for this Brain Injury Research



This XNAT deployment is, in practice, a constellation of computing hardware installed in the MCW Research Computing Center. Three separate servers are each running an instance of XNAT, including a gateway server for data transfers with off-site collaborators and a pair of servers to host redundant XNAT instances of the central database. Images in the central database are stored on an 1.2 PB Isilon storage system, which is backed up through snapshots, mirroring to an additional Isilon storage system, and magnetic tape archiving. The XNAT deployment is further designed to offload processing intensive tasks to other resources of the MCW Research Computing Center, including a 538-core MPI cluster, a large (3Tb) memory system, and four general purpose graphical processing unit (GPU) systems, each with four Nvidia K40 GPUs. Each of these computing units are interconnected with 10 gigabit Ethernet, while internal communication for each unit is maintained with infiniband connections. The XNAT servers are further connected to the general MCW network and pass through the Froedtert Hospital firewall for direct DICOM image pushes to the McKesson PACS for over reads of selected image series.

The XNAT deployment is being further extended to support other mTBI studies at MCW, including the Advanced Research Core of the NCAA/DoD CARE project and the locally conducted GE-NFL Head Health Challenge phases I and II. Reciprocally, data to be acquired in ongoing projects will be used to further refine the data handling and processing software deployed in XNAT. Through this work, MCW will ultimately host the definitive sport related concussion imaging database in this XNAT deployment.

A software developer has joined the team to further accelerate the refinement of this XNAT platform and add automation. To streamline the process of imaging over reads by radiologists on this team, the process of sending images to McKesson PACS has been automated such that once an exam is imported, relevant images are parsed, tagged, and transferred to PACS. Additionally, further automation has been achieved in pre-processing imaging data. Diffusion processing pipelines, including geometric distortion correction, registration, and parameter estimation are now launched automatically when data are imported into the database. Similar automated pipelines are in place for the registration of anatomical images to the Montreal Neurological Institute's template. Pipelines for fMRI processing have been deployed on the Research Computing Center cluster to interactively launch more extensive processing. Continuing work will further advance the automation of such processing.

The XNAT deployment in support of this work is archiving imaging data, serving as the single source of truth for both raw and processed data. The pipeline architecture is ensuring rigorous, consistent processing across the large number of scanning sessions. The pipelines further output quantitative quality assurance metrics which enable the objective sorting of data.

What was the impact on other disciplines?

Nothing to Report

What was the impact on technology transfer?

Nothing to report at this time, although we anticipate that our efforts toward building a unique, technologically advanced TBI MRI informatics system has great potential for technology transfer and product deployment in the future. The XNAT platform at MCW has grown to support other large neuroimaging studies focusing on TBI, epilepsy, and Alzheimer's disease.

What was the impact on society beyond science and technology?

The current study proposal enables a fully integrated and comprehensive investigation of a multidimensional set of injury predictor and diagnostic variables such as *pre-injury function* (e.g. cognitive, behavioral, and psychosocial function, genotype), *injury biomechanics and dynamics* (e.g. mechanism, severity, frequency, associated injury), *immediate post-injury characteristics* (e.g. acute biological, structural and functional markers), and *longitudinal follow-up* (e.g. true natural history of biological, physiological and clinical recovery) (see Figure 1).

In parallel, the aims of this proposal align directly with the DoD's priorities to develop evidence-based approaches to improving the medical care, health and welfare of our military service members affected by TBI. The findings of this study are expected to directly impact the current and future state of military medicine relevant to the diagnosis, treatment and prevention of mTBI in military service members. To date, we lack an integrated neurobiopsychosocial model of mTBI in civilians that can effectively guide evidence based approaches to best practice in the diagnosis, assessment and management of persons affected by mTBI.

The proposed work will foster several lines of collaboration with other DoD-funded investigators conducting innovative TBI research, all aimed at informing the broader science of mTBI in military, sports and civilian populations. This study is designed to significantly advance our understanding of mTBI in such a way to not only benefit the military and sports medicine sectors, but also improve care for patients in our society affected by mTBI.

5. CHANGES/PROBLEMS:

Changes in approach and reasons for change

Non-Helmeted Sensor Technology: In collaboration with the ARC HIM Core team, We continue to evaluate all options for non-helmeted sensors focusing on both the safety of athletes and accuracy of data collection. Our team is conducting internal laboratory testing of candidate sensors at MCW, and collaborating with other groups doing the same elsewhere to best inform adoption of viable technologies for field deployment.

Actual or anticipated problems or delays and actions or plans to resolve them

Head Impact Sensor Technology: As noted above, we continue to encounter challenges in identifying non-helmeted head impact sensors that a) have proper level of preliminary validation to support their use in research efforts, b) have a platform for large scale production to meet our needs, and c) are feasible for field use (with acceptable athlete compliance). Prevent has made considerable advancements in sensor durability and usability (via updated control software) over the past year that will allow us to perform field evaluation of this technology during fall 2017.

Non-Contact Controls: In keeping with our common approach, we will continue with our ongoing recruitment of contact sport controls and do our heaviest recruitment of non-contact sport controls in the winter and spring sports seasons. We do not anticipate any difficulty meeting our targeted samples sizes for the study control groups.

Changes that had a significant impact on expenditures

We are currently underspending for this project, due to a combination of factors outlined below. We anticipate that spending for the overall period of performance for the project will come in at budget. The following changes had an impact on spending during the current reporting period:

- Salaries & Fringe
    - We did not conduct baseline testing in Spring 2015, 2016, or 2017 which resulted in a surplus of baseline technician hours.
    - The biomechanics technicians require less time to manage only one head impact sensor system at their respective sites.
    - The fringe benefit rates for MCW have changed throughout the course of the project.

- Equipment
    - Funds will be used over year 4 to pay for Isilon server purchase.
- Supplies
    - Other than a small amount to purchase i1 mouth guard system and Prevent mouthguards, the majority of funds budgeted for non-helmeted sensor systems have not been used.
    - Many of the blood biomarker assays will be run in year 4 of the project on the complete dataset.
- Subcontracts
    - Banyan subcontract period of performance did not start until Jan 1, 2015. Costs were shifted into years 2-3.

Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents

Significant changes in use or care of human subjects

- Significant Amendments submitted to MCW IRB:
    - none during this reporting period
- Reportable Events submitted to MCW IRB:
    - none during this reporting period
- PMHS testing submitted to VA Research and Development Committee
    - PMHS testing protocol of head impact measurement sensors registered with Zablocki VAMC, Approved by the Subcommittee for Research Safety on Mar 4, 2016 and approved by the Research and Development Committee and authorized by Associate Chief of Staff for Research and Development on Apr 4, 2016, approved by HRPO on May 27, 2016

Significant changes in use or care of vertebrate animals

Not applicable

Significant changes in use of biohazards and/or select agents

Not applicable

6. PRODUCTS:

- **Publications, conference papers, and presentations**

Journal publications

Meier TB, Nelson LD, Huber DL, Hayes RL, McCrea MA. (2017). Prospective assessment of acute and sub-acute blood markers of brain injury following sport-related concussion. J Neurotrauma. Advance online publication, doi: 10.1089/neu.2017.5046

Shah A, Stemper BD, Chiariello R, Wild A, McCrea M. (2017). Influence of subconcussive head impact exposure in onset of concussion among high school and division III college football players. Biomed Sci Instrum 54: 1-6.

Shah A, Murtha J, Humm J, Sjoquist D, Chiariello R, LaRoche A, Stemper B, McCrea M. (2016). Comparison of Head Impact Measurement Data Collected During Routine Participation of Division III College Football Players. Biomed Sci Instrum 53:1-6.

Books or other non-periodical, one-time publications

Nothing to report for the current funding period

Other publications, conference papers, and presentations

Guzowski N, McCrea MA, Nelson LD. (2017). Head-to-head comparison of popular clinical assessment tools used in the management of sport-related concussion (SRC). J Neurotrauma, 34(13): A-1-A-163.1 [Published abstract]

Huber D, McCrea M, Nelson LD. (2017). Application of an activity tracker and mobile application to track activity versus rest following sport-related concussion. J Neurotrauma, 34(13): A-1-A-163.1. [Published abstract and oral conference presentation]

Huber, D, Thomas, D, Danduran, M, Meier, T, McCrea, MA, Nelson, LD. Leveraging mobile technologies to assess athletes' activities after sport-related concussion. Poster presented at the Milwaukee Regional Research Forum (MRRF); Oct 24, 2016, Milwaukee, WI.

Klotz A, Ranson J, Stember, B, Shah A, Nelson LD, McCrea MA. (2017). Pre-injury personality traits predict incidence of concussion in high school and collegiate football athletes. J Neurotrauma, 34(13): A-1-A-163.1. [Published abstract]

McCrea M. Future Directions in TBI Research: Leveraging Sports Concussion Research Toward a Neurobiopsychosocial Model. Presentation at the University of Calgary; February 27, 2016, Calgary, CA.

McCrea M. Advances in the Neurobiology of Concussion. Presentation at the International Brain Injury Association Congress; March 1, 2016, The Hague.

McCrea M. State of the Science in Sport-Related Concussion: How Far Have We Come and Where Do We Go Next? Presentation at the Sports Neuropsychology Society Annual Concussion Symposium; April 30, 2016, Houston, TX.

McCrea M. Neurobiopsychosocial Model of Concussion Recovery. Presentation at the American Academy of Neurology Sports Concussion Conference; July 8, 2016, Chicago, IL.

McCrea M, Giza C. The New Neurometabolic Cascade and A Comprehensive Model of Concussion; Looking to Science to Drive Clinical Practice. Presentation at the National Academy of Neuropsychology Conference; November 6, 2015, Austin, TX.

McCrea M, Giza C. Modern Advances in Mild Traumatic Brain Injury: From Basic Science to Clinical Translation. Presentation at the American Academy of Clinical Neuropsychology Conference; June 10, 2016, Chicago, IL.

McCrea M, Iverson G. Mild Traumatic Brain Injury and Postconcussion Syndrome: How Does the Science Translate to Clinical Practice? Presentation at the International Neuropsychological Society Conference; February 4, 2016, Boston, MA.

Meier TB, Nelson LD, Huber DL, Hayes RL, McCrea MA. Prospective assessment of acute and sub-acute blood markers of brain injury following sport-related concussion. Data blitz and poster presented at the American Academy of Neurology 2016 Sports Concussion Conference; July 8-10, 2016, Chicago, IL.

Shah A, Chiariello R, LaRoche A, Stemper B, McCrea M. Project Head to Head II: Year one review. Poster presented at the Annual National Neurotrauma Symposium; June 26-29, 2016, Lexington, KY.

Shah A, Stemper B, Chiariello R, LaRoche A, Wang Y, Nelson L, McCrea M. Role of subconcussive head impacts in pre- and postseason changes in SCAT3 scores. Poster presented at the 46th Annual Meeting of the Society for Neuroscience, November 12-16, 2016, San Diego, CA.

Shah A, Stemper B, Chiariello R, Wild A, McCrea M. Role of subconcussive head impact exposure in the onset of concussion. Poster presented at the 12th World Congress on Brain Injury, March 29-April 1, 2017 New Orleans, LA.

Shah A, Stemper B, LaRoche A, Wang Y, Chiariello R, Nelson L, McCrea M. Correlation between significant subconcussive head impact exposure and post-season clinical changes in football players. Poster presented at t the American Academy of Neurology 2016 Sports Concussion Conference; July 8-10, 2016, Chicago, IL.

Shah AS, Stemper BD, Murtha JK, Chiariello RA, Humm JR, LaRoche A, McCrea M. Subconcussive head impact exposure for concussed and non-concussed division III football athletes. Conference paper and presentation at the Summer Biomechanics, Bioengineering and Biotransport Conference; June 29-July 2, 2016, National Harbor, MD.

Wang Y, Nelson L, LaRoche A, Nencka A, McCrea M. Dynamic changes of cerebral blood flow during acute and subacute stages of sports-related concussion. Data blitz and poster presented at the American Academy of Neurology 2016 Sports Concussion Conference; July 8 -10, 2016, Chicago, IL.

Wang Y, Nelson L, Nencka A, Meier T, McCrea M. Detecting effects of subconcussive impact on brain functioning using advanced perfusion MRI. Presentation at the 12th World Congress on Brain Injury, March 29-April 1, 2017, New Orleans, LA.

Wild A, Ranson J, McCrea M, Nelson L. (2017). Pre-injury somatic complaints and negative emotionality predict symptom recovery after sport-related concussion. J Neurotrauma, 34(13): A-1-A-163.1 [Published abstract]

- **Website(s) or other Internet site(s)**

Nothing to report for the current funding period

- **Technologies or techniques**

Please see section 4 (Impact) above on MR imaging informatics platform technologies developed as part of this effort.

- **Inventions, patent applications, and/or licenses**

Nothing to report for the current reporting period

- **Other Products**

1. REDCap database built for clinical data collection, being refined for MR, head impact measurement, and blood/genetic data.
    a. Our REDCap database for this study will be leveraged to facilitate a project led by the NINDS toward development of Common Data Elements (CDE) for sport-related concussion.
2. XNAT database platform developed for neuroimaging raw data.
3. Custom database platform designed for head impact measurement raw data.
4. EMC Isilon server set up for data storage.
5. Additional studies: See Appendix B for separately funded studies that will add to the neurobiopsychosocial model of concussion, utilizing the infrastructure of this study

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

What individuals have worked on the project?

Our investigative team for the current project includes clinical and scientific experts within and across all core elements of the study, including clinical, head impact measurement, neuroimaging, biomarkers, and genetic testing. In addition to our key personnel, we have engaged subject matter experts from the ARC investigative team to ensure proper linkage between the two projects for purposes of protocol synchronization and eventual data integration. The following list includes all personnel contributing to work associated with the current project, regardless of funding source.

Name	Project Role	Percent Effort	Contribution to Project
Michael McCrea, PhD	PI	25%	Oversight of project, responsibility for scientific integrity, operational execution, fiscal performance
Lindsay Nelson, PhD	Co-I, Clinical Core	20%	Project design and execution; Database engineering and refinement of clinical protocol
Timothy Meier, PhD	Neuroscience Faculty, MRI & Biomarker Cores	25%	Implementation of protocol for multi-modal MRI data and biomarker acquisition, processing, storage, integration, and analysis
Jana Ranson, PhD	Clinical Post-doc	45%	Assistance with data management, analysis and dissemination
Andrew Nencka, PhD	Imaging Faculty, MRI Core	11%	Lead technical expert on multi-modal MRI protocol for current study; Development and implementation of protocol for multi-modal MRI data acquisition, processing, storage, integration, and analysis
Shi-Jiang Li, PhD	Co-I, MRI Core	8.5%	Development and implementation of protocol for multi-modal MRI data acquisition, processing, storage, integration, and analysis
Matthew Budde, PhD	Co-I, MRI Core	5%	Development and implementation of protocol for multi-modal MRI data acquisition, processing, storage, integration, and analysis
Kevin Koch, PhD	Imaging Faculty, MRI Core	5%	Technical lead for ARC MRI core and liaison to current study; Development and implementation of protocol for multi-modal MRI data acquisition, processing, storage, integration, and analysis

L. Tugan Muftuler, PhD	Imaging Faculty, MRI Core	5%	Development and implementation of protocol for multi-modal MRI data acquisition, processing, storage, integration, and analysis
Yang Wang, MD, PhD	Imaging Faculty, MRI Core	5%	Development and implementation of protocol for multi-modal MRI data acquisition, processing, storage, integration, and analysis
Ron Hayes, PhD	Co-I, Banyan Biomarkers, Biomarker Core	5%	Development and implementation of protocol for biomarker collection, processing, storage, integration, and analysis
Brian Stemper, PhD	Co-I, Head Impact Measurement Core	23%	Co-lead of ARC head impact measurement (HIM) core; assist in development and implementation of protocol for head impact measurement data acquisition, processing, storage, integration, and analysis
Alok Shah, MS	Engineer, Head Impact Measurement Core	31%	Development and implementation of protocol for HIM data acquisition, processing, storage, integration, and analysis
John Humm	Engineer, Head Impact Measurement Core	2.5%	Assist in development and implementation of protocol for HIM data acquisition, processing, storage, integration, and analysis
Jennifer Hill, MA, CCRC	Program Manager, Project Coordinator	25%	Operational and fiscal management of project
Katie Krahn	Program Coordinator	35%	Support project functions related to participant scheduling, reimbursement, inventory management
Robyn Furger, MA CCRC	Research Coordinator	10%	Assisting in protocol planning and operations, clinical data collection and entry
Alexa Wild	Research Assistant	75%	Assisting in protocol planning and operations, clinical data collection and entry
Amy Nader	Research Assistant	27%	Clinical data collection and entry
Nicholas Guzowski	Research Assistant	54%	Clinical data collection and entry
Anna Klotz, LAT	Research Assistant	10%	Clinical data collection and entry

Hannah Bartels	Research Assistant	30%	Clinical data collection and entry
Alexander Kirk	Research Assistant	40%	Clinical data collection and entry
Georgia Ristow	Research Assistant	40%	Clinical data collection and entry
Daniel Huber	Research Technologist	63%	FITBIR liaison and data quality specialist
Rachel Chiariello	Research Technologist	23%	Development of HIM data pipeline and injury identification
Lezlie Espana	Research Technologist	27%	MRI data quality assurance and processing
Habib Al Saleh, PhD	Research Scientist	25%	MRI data quality assurance and pipeline
Brad Swearingen	Programmer Analyst	15%	MRI pipeline construction and maintenance
Jacqueline Dickmann	Lab Technician	25%	MRI data quality assurance and pipeline
William McCuddy	Lab Technician	25%	MRI data quality assurance and pipeline

Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?

Additions to McCrea Other Support

Advancing a Healthier Wisconsin – Research and Education Program
Accessing Cerebrovascular Alterations During Recovery After Sports-Related Concussions (SRC)
PI: Y. Wang
2/1/17-1/31/19
The overarching goal of this proposal is to advance our knowledge of the window of cerebral vulnerability by identifying key neurophysiological mechanisms underlying brain recovery after SRC and develop objective imaging assessments to accurately assess these changes over time.
Role: Co-Investigator, 0.60 calendar months

National Football League
Role of Rehabilitation in Concussion Management: A Randomized, Controlled Trial
Co-PIs: J. Register-Mihalik, K. Guskiewicz, M. McCrea
5/1/16-4/30/19
The goal of this project is to conduct a randomized clinical trial to yield preliminary data on the added benefits of active rehabilitation during recovery after SRC in professional and amateur athletes.
Role: Co-PI, 0.52 calendar months

What other organizations were involved as partners?

Organization Name	Location	Contribution to the Project
Froedtert Hospital	Milwaukee, WI	Facilities
Zablocki VA Medical Center	Milwaukee, WI	Facilities, Collaboration
Banyan Biomarkers, Inc.	Alachua, FL/San Diego, CA	Collaboration
Indiana University	Indianapolis, IN	Collaboration
Carroll University	Waukesha, WI	Facilities, Collaboration
Concordia University of Wisconsin	Mequon, WI	Facilities, Collaboration
Carthage College	Kenosha, WI	Facilities, Collaboration
Wisconsin Lutheran College	Milwaukee, WI	Facilities, Collaboration
Franklin High School	Franklin, WI	Facilities, Collaboration
Marquette University High School	Milwaukee, WI	Facilities, Collaboration
Wauwatosa East High School	Wauwatosa, WI	Facilities, Collaboration
Whitefish Bay High School	Whitefish Bay, WI	Facilities, Collaboration

8. SPECIAL REPORTING REQUIREMENTS

QUAD CHARTS:
Please see Quad Chart on following page.

Comprehensive study of acute effects and recovery after concussion

Log No: 13114003

Award No: W81XWH-14-1-0561

PI: Michael McCrea, PhD, ABPP **Org:** The Medical College of Wisconsin, Inc. **Award Amount:** $6.15M

Study Aims

In a prospective study of high school and low level collegiate athletes :

•Conduct advanced, multimodal MRI studies at multiple time points during the acute and subacute phase after mTBI.

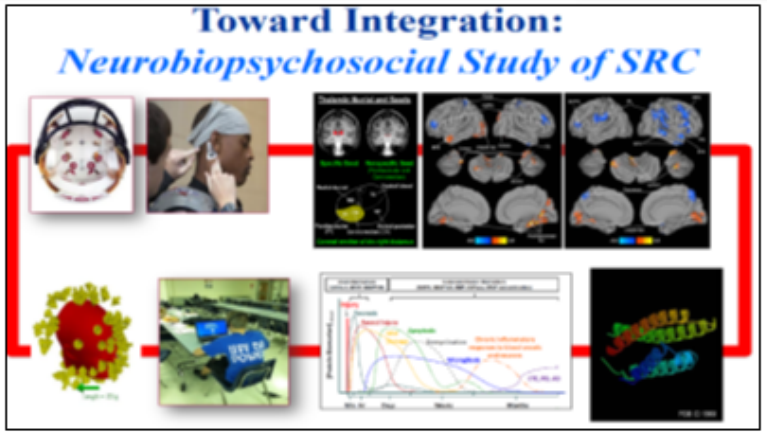
• Collect and analyze blood biomarkers at baseline and multiple time points during the acute and subacute phase after concussion.

• Instrument high school and collegiate athletes with the HIT System and/or non-helmet head impact sensors.

• Conduct genetic testing in our pre-exposure baseline assessments of athletes.

Approach

This study enables a fully integrated and comprehensive investigation of a multidimensional set of injury predictor and outcome variables such as *pre-injury function* (e.g. cognitive, behavioral, and psychosocial function, genotype), *injury biomechanics and dynamics* (e.g. mechanism, severity, frequency, associated injury), *immediate post-injury characteristics* (e.g. acute biological, structural and functional markers), and *longitudinal follow-up* (e.g. true natural history of biological, physiological and clinical recovery).



This study will investigate the correlation between multi-dimensional predictor and outcome variables associated with mTBI from a fully neurobiopsychosocial perspective in a common injured sample and single study design.

Timeline and Cost

Activities CY	14	15	16	17	18
Project Contracting & Regulatory					
Operationalize Protocol					
Data Collection					
Data Management, Analysis & Dissemination					
Estimated Budget ($M)	**$0.5**	**$1.91**	**$1.99**	**$1.45**	**$0.3**

Updated: 11/01/2017

Goals/Milestones

Major Task: **Project Contracting & Regulatory**

- CPR and Amendments submitted to MCW IRB & HRPO

Major Task: **Operationalize Protocol**

- Ongoing protocol refinement within each core area as needed

Major Task: **Data Collection**

- Enrollment: To date, 1,154 athletes enrolled at baseline
- Accrual: 86 concussed athletes and 99 controls in post injury protocol
- Enrollment and accrual ahead of schedule, to allow oversampling, controlling for slight attrition and powering multi-dimensional analysis

Major Task: **Data Management, Analysis & Dissemination**

- Continued progress of data pipeline and analysis for each core area
- Data regularly submitted to FITBIR this year; dissemination/publication of findings in process

Comments/Challenges/Issues/Concerns

- Project progressing in achieving study aims on course, on schedule

Budget Expenditure to Date

Projected Expenditure: $ 5.76M *Actual Expenditure*: $ 4.22M

Burn-rate to equalize based on timing of project expenses

9. APPENDICES:

Table 2. Study Technical Objectives and Specific Aims

The current study proposal enables a fully integrated and comprehensive investigation of a multidimensional set of injury predictor and diagnostic variables such as *pre-injury function* (e.g. cognitive, behavioral, and psychosocial function, genotype), *injury biomechanics and dynamics* (e.g. mechanism, severity, frequency, associated injury), *immediate post-injury characteristics* (e.g. acute biological, structural and functional markers), and *longitudinal follow-up* (e.g. true natural history of biological, physiological and clinical recovery).

ADVANCED NEUROIMAGING BIOMARKERS:	***Technical Objective***: To conduct advanced, multimodal MRI studies at multiple time points during the acute and subacute phase after mTBI. ***Specific Aims***: 1. Characterize the physiological effects of acute mTBI on brain structure and function. 2. Determine how the natural time course of neurophysiological recovery after mTBI compares to the time course of clinical recovery. 3. Determine the window of neurophysiological vulnerability after mTBI, during which the brain is at risk of secondary or cumulative injury.
BLOOD BIOMARKERS:	***Technical Objective***: To collect and analyze blood biomarkers at baseline and multiple time points during the acute and subacute phase after concussion. ***Specific Aims***: 1. Measure the direct effects of acute mTBI on brain biology. 2. Correlate the sensitivity and specificity of brain biomarkers with other measures of the effects of mTBI (symptom recovery, cognitive testing, balance assessment, neuroimaging). 3. Determine how the time course of biological recovery after mTBI compares to the time course of clinical recovery.
HEAD IMPACT SENSORS:	***Technical Objective***: To dually-equip high school and collegiate athletes with the HIT System and/or non-helmet head impact sensors. ***Specific Aims***: 1. Cross validate multiple head impact sensors systems used in mTBI research. 2. Measure the relationship between biomechanical metrics of head impact location and magnitude (e.g., rotational acceleration) and measures of clinical and physiological effects of acute mTBI. 3. Determine the minimum biomechanical threshold sufficient to cause mTBI. 4. Determine the clinical effects of subconcussive head impact exposure from contact and collision sports on neurocognitive function through comparison to a noncontact sport control group not exposed to repetitive head impacts.
GENETIC TESTING:	***Technical Objective*:** To conduct genetic testing in our pre-exposure baseline assessments of athletes. ***Specific Aims*:** 1. Determine the influence of genetics on risk of mTBI. 2. Determine genetic influence on acute recovery and outcome after mTBI. 3. Enable longitudinal study of the influence of genetics on long-term outcome after mTBI in a well characterized cohort of injured and control subjects.

Table 3.
Post-injury assessments completed

Injured Athletes						**Total Visits**
VISIT	**6 hour**	**<48 hour**	**8 day**	**15 day**	**45 day**	
Clinical Testing	56%	100%	96%	89%	89%	338
Blood	56%	99%	95%	88%	86%	333
MRI	-	99%	95%	83%	84%	279
HITS	48%	-	-	-	-	42
# of Subjects who Reached Follow Up Period	86*	84	81	78	64	
Contact Controls						**Total Visits**
VISIT	**6 hour**	**<48 hour**	**8 day**	**15 day**	**45 day**	
Clinical Testing	53%	100%	94%	90%	85%	275
Blood	97%	100%	93%	88%	83%	302
MRI	-	99%	94%	88%	85%	237
HITS	45%	-	-	-	-	33
# of Subjects who Reached Follow Up Period	68	68	67	63	60**	
Non-Contact Controls						**Total Visits**
VISIT	**6 hour**	**<48 hour**	**8 day**	**15 day**	**45 day**	
Clinical Testing	100%	100%	100%	97%	100%	154
Blood	100%	97%	94%	97%	97%	150
MRI	-	94%	100%	94%	97%	119
# of Subjects who Reached Follow Up Period	31	31	31	31	31	

Average hours to 6 hour evaluation = 5.3. Average hours to 48 hour evaluation = 31.7
*2 injured athlete only received 6hr blood draw.
**2 Contact Controls injured before 45 day.

APPENDIX B
Additional studies with separate funding; currently approved

MEG Biomarkers of mTBI
PI: Lin Nelson, PhD Period of Performance: 2/1/16-2/28/17
Source: Advancing a Healthier Wisconsin – Research and Education Program
Total Award: $25,000

Concussion is a highly prevalent injury that causes temporary, and sometimes chronic, impairment in several functional abilities. Although major strides have been made to understand the course of clinical recovery following injury, it remains difficult to objectively diagnose concussion due to reliance on patients' reports of nonspecific subjective symptoms. Furthermore, no empirically supported treatment exists to improve patients' recoveries and mitigate risk of chronic problems. Consequently, there is a need to identify more objective biomarkers of concussive injury and to map the time course and predictors of neurophysiologic recovery such that empirically supported diagnostic and treatment protocols can be developed for concussed patients. Given its high temporal and spatial resolution, magnetoencephalography (MEG) has been proposed as a tool that may be uniquely suited to advance our understanding of the neurophysiologic effects of concussion. Although a small body of research supports it as promising tool in the study of brain injured populations, the literature is limited heterogeneous samples of patients who are far beyond the acute post-injury period, making it difficult to link MEG abnormalities to concussive injury per se. The aim of this study was to identify MEG biomarkers of acute concussion. Twenty eight contact sport athletes (13 conconcussed, 15 nonconcussed controls) underwent MEG assessment at one week postinjury. Subjects were recruited from Project Head to Head 2 (W81XWH-14-1-0561), allowing us to capitalize on the recruitment infrastructure, clinical assessment, and multimodal MRI data being collected through this study. Analyses currently underway will explore the degree to which both resting and task-elicited MEG variables are sensitive to concussive injury. The findings will significantly enhance knowledge about the degree to which MEG contributes to the assessment of concussion. Findings will facilitate application for extramural funding to chart the neuromagnetic and neurophysiologic mechanisms underlying response to and recovery following concussive injury.

CTSI2016: Association Between Post-Concussive Activity and Recovery
PI: Lin Nelson, PhD Period of Performance: 4/1/16-3/31/17
Source: Advancing a Healthier Wisconsin – Research and Education Program/CTSI
Total Award: $50,000

Significant advances have been made to understand the natural course of clinical and neurophysiologic recovery after sport-related concussion (SRC). Although experts recommend that athletes assume some degree of cognitive and physical rest in the acute period post-SRC, almost no data are available regarding the effects of post-concussive activities on athletes' recovery. Pre-clinical data indicate that physical activity too soon post-injury is harmful for neural recovery, yet activity performed later is beneficial. The aim of proposed study is to advance our understanding of the relationship between post-injury activities and measures of clinical and neural recovery in humans. The project will use a commercially-available device (Fitbit) and locally developed smart phone application to obtain detailed, real-time data about

athletes' (recruited from W81XWH-14-1-0561) postconcussive activities in the acute post-concussive period in order to establish the degree to which concussion affects athletes' typical activity levels, understand the degree of variability among concussed athletes' post-injury activity levels, and to correlate activity data with clinical and neuroimaging-based markers of recovery. Our multidisciplinary investigative team has the extensive clinical and research expertise needed to aggregate these varying types of data and has long contributed to cutting-edge SRC research with high translational value. The study will provide important data regarding the tolerability of these devices with participants and the foundational data necessary to secure extramural funding aimed at developing and validating evidence-based concussion management guidelines.

High-field neuroimaging of mTBI: Investigating the neurophysiological correlates of mild traumatic brain injury using advanced neuroimaging markers in high-field, 7 Tesla scanner
PI: Kevin Koch, PhD Period of Performance: 1/1/15-6/30/16
Source: Daniel M. Soref Charitable Trust
Total Award: $7,500

Investigating the neurophysiological correlates of mild traumatic brain injury using advanced neuroimaging markers in high-field, 7 Tesla scanner. To date, the majority of neuroimaging research in mTBI has been conducted on 3 Tesla (T), or even 1.5T scanners. However, the utilization of higher field 7T MR scanners provides an opportunity to measure the effects of mTBI with higher resolution and improved signal-to-noise ratio (van der Kolk, et al., 2013). These advantages of 7T imaging could potentially provide a more detailed understanding of the pathophysiological effects of mTBI.

Our research team has extensive experience using various neuroimaging techniques to assess the acute and chronic effects of mTBI in studies performed here at MCW and elsewhere. For example, we have documented significant abnormalities in white matter, including increased fractional anisotropy (Meier, et al., 2016a) and increased axial kurtosis (unpublished data) at several time points post-concussion. In addition, we have documented reduction of CBF within the first week post-concussion in athletes relative to healthy athletes (Meier, et al., 2015; Wang, et al., 2015). Furthermore, we have observed both increases and decreases of local functional connectivity using resting state fMRI at one-month post-injury, indicative of prolonged neurophysiological changes due to concussion (Meier, et al. 2016b). Importantly, this work was all performed on scanners with lower field strength (3T), and thus the improved signal-to-noise and higher resolution provided by the 7T will extend upon our previous research and critically advance the field's understanding of the pathophysiological effects mTBI. We will utilize mTBI and control subjects from W81XWH-14-1-0561 6 months post-injury for this study.

Accessing Cerebrovascular Alterations During Recovery After Sports-Related Concussions (SRC):
PI: Yang Wang, MD, PhD Period of Performance: 2/1/17-1/31/19
Source: Advancing a Healthier Wisconsin – Research and Education Program
Total Award: $200,000

Sports-induced concussion (SRC) has recently become a prominent concern, not only in the athletic setting but also in the general population. Clinically, it remains a great challenge to predict how quickly SRC patients recover and how likely they are to develop long-term symptoms, while very little data are available regarding the nature of the neural dysfunction after injury. There is a fundamental gap in understanding of the pathophysiological processes underlying functional recovery in SRC. Moreover, emerging evidence shows persistent neurophysiological abnormalities beyond the point of clinical recovery after SRC, namely the window of cerebral vulnerability (WoCV), during which the brain may remain physiologically compromised and at increased risk for repetitive injury. Ideally, prevention-based return to activity decision-making would be based upon more objective markers of both clinical and physiological recovery, indicating that the WoCV has elapsed and that it is safe to resume activity. Therefore, measurable biological indicators of this WoCV have significant implications for the management of SRC. No such biomarker currently exists for clinical use. The overarching goals of this proposal are to identify key neurophysiological mechanisms underlying brain recovery after SRC and to develop an objective imaging biomarker to accurately assess these changes over time. The primary objective of this project is to characterize regional cerebrovascular reactivity (CVR) and cerebral blood flow (CBF) in SRC patients using a novel multiband and multiecho MRI technique that enables acquisition of arterial spin labeling (ASL) and blood oxygenation level dependent (BOLD) signals simultaneously. In this proof-of principle study, we plan to evaluate 24 concussed college football players three times, 15, 45 days and 6 months post-injury; results will be compared to those of 24 demographically matched non-injury players. The proposed research will likely generate translational impact in clinical practice for SRC. The approach is innovative; utilizing advanced neuroimaging methods to better understand the underlying neurovascular mechanism in SRC. Findings from this study will have important clinical significance, with the potential to enhance the capacity to detect underlying neurophysiological process in SRC, monitor recovery from the injury, and serve as a potential biomarker for response to treatment interventions in the future.

1R03NS100691-01
Clinical Phenotyping of Mild Traumatic Brain Injury (mTBI)
PI: Lin Nelson, PhD Period of Performance: 4/1/17-3/31/19
Source: NIH/NINDS
Total Award: $167,379

Mild traumatic brain injury (mTBI) is a costly injury due to its high prevalence and effects on patients' emotional, cognitive, and occupational functioning. Efforts to identify the neurobiological effects of mTBI and develop effective treatments are hampered by limitations in current operational definitions of the injury. This problem stems from heterogeneity in patients' responses to mTBI and conventions to aggregate diffuse, nonspecific symptoms into a single diagnostic category. Although current clinical and research practices treat mTBI as unitary, emerging evidence indicates that clinical presentation following injury is multidimensional, with distinct elements that may be more informative when measured separately. The proposed R03 project will apply modern quantitative methods to establish distinct clinical phenotypes of mTBI with higher potential to inform translational mTBI research. The aims of the study are to (1) identify the optimal phenotypic model of clinical presentation in both athlete and civilian mTBI patients and (2) test hypotheses regarding sex differences in mTBI phenotypes. The project will

be innovative in its application of diverse, advanced quantitative modeling approaches to identify mTBI phenotypes and to compare multiple groups of interest (males and females, athlete and civilians). The proposed work is made possible by the recent availability of sufficiently large, longitudinal datasets of athletes and civilians with mTBI and the collaboration of our team of investigators with diverse clinical, empirical, and methodological expertise relevant to the proposed project. The findings will be significant in yielding novel phenotypic models that (a) could change how the field diagnoses and classifies mTBI and (b) could yield novel clinical targets with tighter or more consistent linkages to neurobiological systems. The long-term goal of this research is to use the findings derived from this project to accelerate efforts to identify the neurobiological mechanisms underlying mTBI and to develop personalized interventions to maximize patients' recoveries from mTBI.

1R21NS099789-01A1
Inflammation and Kynurenine Metabolites in the Acute Sequelae of Concussion
PI: Tim Meier, PhD Period of Performance: 7/1/17-6/30/19
Source: NIH/NINDS
Total Award: $443,249

There is a pressing need to identify molecular pathways underpinning the acute effects of mild traumatic brain injury (mTBI) and sport-related concussion (SRC). This information will ultimately lead to the development of objective, prognostic biomarkers to enable a more evidence-based approach to the clinical management of mTBI/SRC. Inflammatory cytokines known to be elevated following brain injury lead to the production of kynurenine pathway (KP) metabolites that have neuroprotective or neurotoxic effects on the brain. The effects of SRC on KP metabolites and their inflammatory mediators, however, remain unknown. The objective of this proposal is to evaluate one potential pathophysiological mechanism behind acute brain and behavioral changes following SRC. The central hypothesis is that SRC leads to inflammation-induced increases in neurotoxic KP metabolites that are associated with short-term changes in behavior and functional connectivity of the hippocampus and medial prefrontal cortex (mPFC). The rationale for this research is that understanding metabolic changes following SRC will aid development of prognostic biomarkers and eventual development of therapeutic strategies for patients with SRC. To test our hypotheses, we will leverage blood, clinical, and neuroimaging data from an existing federally funded project on high school and collegiate athletes. Clinical data and blood is available at pre-injury baseline and at 6 hours, 2 days, 8 days, 15 days, and 45 days post-injury in football players. Neuroimaging data is available at 2, 8, 15, and 45 days post-injury. Non-injured football players with identical time points serve as controls and non-contact sport athletes with identical time points serve as additional controls. We will address the following specific aims: 1) Prospectively establish the time course of changes in neurotoxic KP metabolites and their inflammatory mediators from pre- to multiple post-concussion visits, 2) Determine the extent to which these metabolites are associated with postconcussion symptom reporting and outcome, and 3) Determine the extent to which these metabolites are associated with changes in functional connectivity of the mPFC and hippocampus. This project represents a scientifically innovative approach to study SRC by prospectively investigating the role of a well-described metabolic pathway as a potential final common pathway in the pathogenesis of the acute effects of SRC and is significant because it will stimulate a new line of programmatic research aimed at identifying physiological targets for therapeutic treatment of SRC.